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Docket: 2373 USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Zhang Examiner: Unassigned

Serial No: 60/136,731 Art Group Unit: Unassigned

Filed: May 29, 1999

For: Bioabsorbable Blends and Surgical Articles Therefrom

APPLICATION TRANSMITTAL LETTER

Asst. Commissioner For Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the [x] utility [ ] design patent application in this case including:

1. [ ] This application is a [ ] Continuation; [ ] Divisional [ ] Continuation in Part of prior application

2. [x] This application claims priority from Provisional Application Serial No. 60/136,731 filed on May 29, 1999.

3. [ ] The application consisting of 12 pages (including specification, claims and abstract).

4. [ ] 0 sheet(s) of drawings is enclosed. The drawings are:

   a. [ ] formal; or
   b. [ ] informal; formal drawings will be submitted in due course.

5. [ ] A signed declaration and power of attorney is enclosed.

6. [x] A declaration and power of attorney is not enclosed at this time since it has not been executed by the inventor(s). A signed declaration and power of attorney will be submitted in due course.
   The inventor(s) is/are Guanghui Zhang.

7. [ ] An Assignment of the invention to _____ is enclosed. Please record the Assignment and return it to the undersigned.

8. [ ] The Application filing fee is calculated below.

	No. Filed	No. Extra*	Rate:	Fee
Basic Fee:				$ 760.00
Total Claims:	18 - 20		x 18.00	$ 0.00
Indep Claims:	1 - 3		x 78.00	$ 0.00
[ ] Multiple Dependent Claims Presented		+ $270.00		$ 0.00
			TOTAL:	$ 760.00

9. [x] Please charge Deposit Account No. 21-0550 in the amount of $ 760.00 which includes filing fee and recordation fee). **TWO DUPLICATE COPIES OF THIS PAPER ARE ENCLOSED.**

10. [x] The Commissioner is hereby authorized to charge any additional fees which may be required for this application, or credit any overpayment to Deposit Account No. 21-0550. **TWO DUPLICATE COPIES OF THIS SHEET ARE ENCLOSED.**

Respectfully submitted,

Date: May 30, 2000

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Docket No. 2373 USA

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Applicant: Zhang

Serial No: 60/136,731 Examiner:Unassigned

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Title: Bioabsorbable Blends and Surgical articles Therefrom

CERTIFICATE OF EXPRESS MAILING

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Bioabsorbable Blends and Surgical Articles Therefrom

TECHNICAL FIELD

Bioabsorbable blends of materials including glycolide, lactide, caprolactone, dioxanone, trimethylene carbonate, alkylene glycols, esteramides, etc., and polymers and copolymers thereof with cyanoacrylates are described. Processes for making the polymers and surgical articles made totally or in part from such polymers, including sutures, are also described.

BACKGROUND OF THE INVENTION

Cyanoacrylate based tissue adhesives are well known in the art for use in wound closure. It is thought that such adhesives can be applied without the use of a local anesthetic and without the trauma caused by a needle and suture. However, commercially available products such as Dermabond, commercially available from Closure Medical, Raleigh, North Carolina, and Indermill, commercially available from Davis & Geck, are not bioabsorbable and hence are not suitable for internal applications.

Therefore, it would be advantageous to provide a bioabsorbable tissue adhesive. Such tissue adhesives would not only be of use in external applications, but also could be used in more invasive procedures such as abdominal or cardiothoracic surgery.

SUMMARY OF THE INVENTION

It has now surprisingly been found that a cyanoacrylate and a bioabsorbable component derived from glycolide, lactide, caprolactone, dioxanone, trimethylene carbonate, alkylene glycols, esteramides, etc., and polymers and copolymers thereof, can be blended together to form a material that is bioabsorbable and

provides excellent flexibilty and adhesive properties, while maintaining acceptable viscosity and curing times when applied to mammalian tissues.

In one embodiment blends used in forming such a tissue adhesive are prepared by blending about 5 to about 60 percent by weight of a bioabsorbable component with about 95 to about 40 percent by weight of a cyanoacrylate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The bioabsorbable blend may be prepared by conventional methods well known in the art. Suitable blends can be prepared by blending about 5 to about 60 percent by weight of a bioabsorbable component with about 95 to about 40 percent by weight of a cyanoacrylate. Preferrably the blend may include about 10 to about 40 percent by weight of a bioabsorbable component and about 90 to about 60 percent by weight of a cyanoacrylate. In one embodiment the blend may include about 12 to about 20 percent by weight of a bioabsorbable component and about 88 to about 80 weight percent of a cyanoacrylate. It is to be understood that as used herein the term "bioabsorbable component" shall not imply that the cyanoacrylate component is or is not bioabsorbable.

Suitable cyanoacrylates include branched or straight chain C_4-C_{12} cyanoacrylates, such as butyl cyanoacrylates (such as n-butyl cyanoacrylate, perfluoro butyl cyanoacrylate, and tert-butyl cyanoacrylate), pentyl cyanoacrylate, hexyl cyanoacrylate, octyl cyanocarylates (such as n-octyl cyanoacrylate and 2-octyl cyanoacrylate); straight or branched chain alkyloxyalkyl cyanoacrylates; straight or branched chain cyanoacrylates having multiple ether or ester linkages therein; and ethylenically unsaturated cyanoacrylates with functional groups such as cyclic alkanes.

Suitable bioabsorbable materials include glycolide, lactide, caprolactone, dioxanone, trimethylene carbonate, alkylene glycols, esteramides, etc., and blends, polymers and copolymers thereof. Suitable bioabsorbable copolymers include both linear and star shaped copolymers derived from epsilon-caprolactone and

glycolide, lactide, dioxanone, and / or trimethylene carbonate initiated with an alchohol such as dodecanol, a diol such as diethylene glycol, or a polyol such as glycerol, pentaerythritol, or mannitol, such as those disclosed in U.S. Patent Number 5,543,218. A "predominant amount" as defined herein is an amount greater than about 50 weight percent.

Suitable caprolactone containing polymers for use in the bioabsorbable component of the blend described herein include copolymers which can be synthesized by well known techniques; see, for example Principles of Polymerization, George Odian, III Edition; 1991 pp. 569-573, the contents of which are incorporated herein by reference. Suitable caprolactone containing copolymers can be obtained by polymerizing a major amount of epsilon-caprolactone and a minor amount of at least one other copolymerizable monomer or mixture of such monomers in the presence of a polyhydric alcohol initiator. The polymerization of these monomers contemplates all of the various types of monomer addition, i.e., simultaneous, sequential, simultaneous followed by sequential, sequential followed by simultaneous, etc.

Suitable monomers which can be copolymerized with epsilon-caprolactone include glycolide, lactide, p-dioxanone and trimethylene carbonate.

Suitable polyhydric alcohol initiators include glycerol, trimethylolpropane, 1,2,4-butanetriol, 1,2,6-hexanetriol, triethanolamine, triisopropanolamine, erythritol, threitol, pentaerythritol, ribitol, arabinitol, xylitol, N,N,N',N'-tetrakis(2-hydroxyethyl)ethylenediamine, N,N,N',N'-tetrakis(2-hydroxypropyl)ethylenediamine, dipentaerythritol, allitol, dulcitol, glucitol, altritol, iditol, sorbitol, mannitol, inositol, and the like. The polyhydric alcohol initiator is generally employed in small amounts, e.g., from about 0.5 to about 5, and preferably from about 0.1 to about 2, weight percent of the total monomer mixture.

The copolymer for use in the bioabsorbable component of the blend described herein can contain from about 70 to about 98, and preferably from about 80 to about 95, weight percent epsilon-

caprolactone-derived units, the balance of the copolymer being derived from the other copolymerizable monomer(s). The inherent viscosity of the copolymer generally ranges from about 0.10 to about 0.60, and preferably from about 0.20 to about 0.50, dl/g when measured in chloroform at a concentration of 0.2500 g/dl at 30°C.

The bioabsorbable component may then be blended with the cyanoacrylate any well known conventional technique.

In another embodiment the bioabsorbable composition is a copolymer including epsilon-caprolactone and lactide. Suitable caprolactone / lactide copolymers include random copolymers containing about 40 to about 90 percent by weight epsilon-caprolactone and about 60 to about 10 percent by weight lactide. Such polymers can be synthesized using well known techniques such those described in Principles of Polymerization, George Odian, III Edition; 1991 pp. 569-573, the contents of which are incorporated herein by reference.

It is further contemplated that one or more medico-surgically useful substances can be incorporated into the presently disclosed blends, e.g., those medico-surgically useful substances which accelerate or beneficially modify the healing process when particles are applied to a surgical repair site. So, for example, the tissue adhesive can carry a therapeutic agent which will be deposited at the repair site. The therapeutic agent can be chosen for its antimicrobial properties, capability for promoting repair or reconstruction and/or new tissue growth. Antimicrobial agents such as broad spectrum antibiotic (gentamycin sulfate, erythromycin or derivatized glycopeptides) which are slowly released into the tissue can be applied in this manner to aid in combating clinical and sub-clinical infections in a tissue repair site. To promote repair and/or tissue growth, one or several growth promoting factors can be introduced into the tissue adhesives, e.g., fibroblast growth factor, bone growth factor, epidermal growth factor, platelet

derived growth factor, macrophage derived growth factor, alveolar derived growth factor, monocyte derived growth factor, magainin, and so forth. Some therapeutic indications are: glycerol with tissue or kidney plasminogen activator to cause thrombosis, superoxide dimutase to scavenge tissue damaging free radicals, tumor necrosis factor for cancer therapy or colony stimulating factor and interferon, interleukin-2 or other lymphokine to enhance the immune system.

In order that those skilled in the art may be better able to practice the compositions and methods described herein, the following examples are given as an illustration of the preparation of blends herein. It should be noted that the invention is not limited to the specific details embodied in the examples.

Example 1

Dry glycolide (222 grams) and distilled epsilon-caprolactone (2000 grams), were added to a reactor along with 0.44 grams of distilled stannous octoate and 2.2 grams of mannitol. The mixture was dried for about 6 hours with agitation under flow of nitrogen. The reactor temperature was then set at 160°C and polymerization was conducted with stirring under a nitrogen atmosphere for about 20 hours.

The reaction product was then isolated, comminuted, and treated to remove residual reactants using known techniques. The treatment to remove residual reactants occurred at 90°C for 48 hours under vacuum.

Example 2

About 200 milligrams of the copolymer of Example 1 were added to a vial containing about 1 milliliter of n-butyl

cyanoacrylate. The vial was then shaken for about 10 hours. The reaction product was then sampled.

Example 3

About 200 milligrams of the copolymer of Example 1 were added to a vial containing about 1 milliliter of octyl cyanoacrylate. The vial was then shaken for about 10 hours. The reaction product was then sampled.

Example 4

Epsilon-caprolactone (20 grams) and lactide (20 grams) were added to a reactor along with 0.008 grams of Stannous Octoate and 0.06 grams mannitol. The mixture was heated and placed in an oven at 165°C for about 48 hours with stirring.

The reaction product was then isolated and treated to remove residual reactants using known techniques. The treatment to remove residual reactants occurred at 90°C for 45 hours under vacuum.

Example 5

About 125 milligrams of the copolymer of Example 4 were added to a vial containing about 1 milliliter of n-butyl cyanoacrylate. The vial was then shaken for about 5 minutes. The reaction product was then sampled.

Example 6

Epsilon-caprolactone (28 grams) and glycolide (12 grams) were added to a polymerization tube along with 0.008 grams of Stannous Octoate and 0.105 grams diethylene glycol. The mixture was heated and placed at 165°C for about 24 hours with stirring.

The reaction product was then isolated and treated to remove residual reactants using known techniques. The treatment to remove residual reactants occurred at 90°C for 48 hours under vacuum.

Example 8

About 125 milligrams of the copolymer of Example 7 were added to a vial containing about 875 milligrams of n-butyl cyanoacrylate. The vial was then shaken for about 10 hours. The reaction product was the sampled.

Example 9

About 32 grams of trimethylene carbonate and about 8 grams glycolide were added to a polymerization tube along with 0.008 grams stannous chloride and about 0.06 grams of mannitol. The mixture was heated and placed in an oven at 165°C for 48 hours.

The reaction product was then isolated and treated to remove residual reactants using known techniques. The treatment to remove residual reactants occurred at 90°C for 48 hours under vacuum.

Example 10

About 125 milligrams of the copolymer of Example 7 were added to a vial containing about 875 milligrams of n-butyl cyanoacrylate. The vial was then shaken for about 10 hours. The reaction product was the sampled.

It will be understood that various modifications may be made to the embodiments disclosed herein. For example, the compositions disclosed herein may be blended withother biocompatible, bioabsorbable, or nonbioabsorbable materials. Therefore, the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifiocations within the scope and spirit of the claims appended hereto.

What is claimed is:

1. A blend comprising at least one bioabsorbable component and a cyanoacrylate component.

2. The blend of claim 1 wherein the bioabsorbable component comprises about 40 weight percent to about 95 weight percent of the blend.

3. The blend of claim 1 wherein the bioabsorbable component comprises about 5 weight percent to about 60 weight percent of the blend.

4. The blend of claim 1 wherein the bioabsorbable component comprises about 10 weight percent to about 40 weight percent of the blend.

5. The blend of claim 1 wherein the bioabsorbable component comprises about 12 weight percent to about 20 weight percent of the blend.

6. The blend of claim 1 wherein the cyanoacrylate component comprises about 40 weight percent to about 95 weight percent of the blend.

7. The blend of claim 1 wherein the cyanoacrylate component comprises about 60 weight percent to about 90 weight percent of the blend.

8. The blend of claim 1 wherein the cyanoacrylate component comprises about 80 weight percent to about 88 weight percent of the blend.

9. The blend of claim 1 wherein the bioabsorbable component is selected from the group consisiting of glycolide, lactide,

trimethylene carbonate, dioxanone, caprolactone, alkylene glycols, esteramides, and copolymers thereof.

10. The blend of claim 1 wherein the bioabsorbable component comprises a copolymer comprising a predominant amount of epsilon-caprolactone and a minor amount of at least one other copolymerizable monomer.

11. The blend of claim 10 wherein the other copolymerizable monomer(s) are selected from glycolide, lactide, trimethylene carbonate and dioxanone.

12. The blend of claim 1 wherein the bioabsorbable component comprises a copolymer comprising a predominant amount of trimethylene carbonate and a minor amount of at least one other monomer copolymerizable therewith.

13. The blend of claim 1 wherein the cyanoacrylate component comprises branched or straight chain C_4-C_{12} cyanoacrylates, straight or branched chain alkyloxyalkyl cyanoacrylates; straight or branched chain cyanoacrylates having multiple ether or ester linkages therein; and ethylenically unsaturated cyanoacrylates with functional groups such as cyclic alkanes.

14. The blend of claim 1 wherein the cyanoacrylate component is selected from the group consisting n-butyl cyanoacrylate, perfluoro butyl cyanoacrylate, tert-butyl cyanoacrylate, pentyl cyanoacrylate, hexyl cyanoacrylate, n-octyl cyanoacrylate, 2-octyl cyanoacrylate.

15. The blend of claim 1 wherein the bioabsorbable component comprises:

a copolymer comprising a predominant amount of epsilon-caprolactone and a minor amount of glycolide; and

the cyanoacrylate component comprises n-butyl cyanoacrylate.

16. The blend of claim 1 wherein the bioabsorbable component comprises:

a copolymer containg units derived from glycolide and epsilon-caprolactone; and

the cyanoacrylate component comprises n-butyl cyanoacrylate.

17. The blend of claim 1 wherein the bioabsorbable component comprises:

a copolymer containg units derived from lactide and epsilon-caprolactone; and

the cyanoacrylate component comprises n-butyl cyanoacrylate.

18. The blend of claim 1 wherein the bioabsorbable component comprises:

a copolymer containg units derived from glycolide and trimethylene carbonate; and

the cyanoacrylate component comprises n-butyl cyanoacrylate.

ABSTRACT

Blends made of bioabsorbable materials including glycolide, lactide, caprolactone, dioxanone, trimethylene carbonate, alkylene glycols, esteramides, etc., and polymers and copolymers thereof with cyanoacrylates are described. Processes for making the polymers and surgical articles made totally or in part from such polymers, including sutures, are also described.